



**Medicine at the Crossroads:
Between Science and Bio-Utopia**

*Transcript of Conference on Regenerative Medicine

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Sulmasy: Let me add my words of welcome and thanks to all of you. It seems like it's taken us about 20 minutes to actually get started, but that's okay, maybe it's given some people some time to get into the room here.

I'm going to use some of the technology here, and use some slides, for the introduction, and, as Lynn said, what I'm going to try to do is just give a basic overview of some of the science and to raise some of the scientific and some of the ethical questions that our panelists will address.

There is a way in which you can think about medicine and its great success, particularly in the 20th Century, as having in series address these two kinds of clinical problems. The first big question that was tackled was infectious diseases. At the turn of the 19th to the 20th Century, the big problems in medicine were infant mortality, tuberculosis and pneumonia. And by the middle of the century, something with public health but largely with the invention of antibiotics, these problems became really fairly easy to solve. When 50% of people who got pneumococcal pneumonia used to die, and now we've got it down to less than 1%, unless we decide not to do other things for them, that's significant.

The second phase we went through after that was that we've been pretty successful in turning what used to be acute lethal diseases basically into chronic diseases. So, people used to die of diabetes. Now we can replace that. They still have long-term complications down the line, but what used to kill them in acute diabetes, particularly type 1, now as a chronic disease that lasts many years, recently with breast cancer the same sort of thing has happened. We've turned it into a chronic disease where instead of killing people in one year, it may take ten to fifteen years.

But the new clinical problem that we face seems to be that biological tissues wear out. All of us who have reached at least middle age begin to have those aches and pains of arthritis, we develop fatty streaks and atherosclerosis in our blood vessels which don't seem to be able to repair themselves, and we know that many of the tissues we have in our bodies lose the ability to repair themselves. So when people have a heart attack, one of the problems is that what replaces the muscle tissue is scarred tissue, not new heart muscle cells. When people have a stroke, the damage seems to be permanent. You can find ways to sort of rewire things around it, get the person to be able to function with the different circuitry, but you don't replace what was damaged by the stroke. With Alzheimer's disease you get the degeneration of certain tissues. With diabetes you lose in fact the ability to create insulin, the hormone that's needed to control blood sugar. And

people have begun to think about aging itself as really a series of accumulation of insults, and the loss of ability to repair these insults.

Now in the 60s, a scientist named Hayflick came to the idea that human cells can only divide a finite number of times. And we know now a little bit more of why this happens. At the ends of our chromosomes, the DNA at the end of them, begins to shorten every single time a cell replicates. Now we know this is associated with a cell's age. There's decreased heat-shock protein, there's increased genetic abnormalities. So when the cells divide, they don't have the same number of chromosomes, what's called polyploidy. There accumulate problems in the mitochondrial DNA inside the cells. There're organelles called mitochondria, there's DNA in those. That begins to develop mutations, and all this seems genetically controlled. There's a difference from species to species, but the same phenomenon seems to occur, so that people realize this may be the explanation for what's been called the rectangularization of the human survival curve.

In the 19th Century, a lot of people died in infancy, children died, and then there was sort of a slow progression as people died of infectious diseases, as they died of some of the degenerative diseases later on. But what we've been successful in really in medicine has not been that the limit has been increased for us so much as more people get closer to the limit and that limit typically may be around 100. People say maybe you could naturally get it up to 110, but you don't see people 150 years old walking around. Medicine hasn't done that, it's just that more people are getting closer to 100 years old because of what we've been able to do.

Now, if the problem has been that we face now all of these degenerative diseases, then regeneration, regenerative medicine is seen as the solution. And people have said, "Well, we can protect cells from degenerating, we can prevent the loss of the regenerative capacity of the cells we have. We might be able to manipulate genes for longevity. We might be able to, and we already do this to some extent, transplant organs, tissues, stem cells, or even clone to make organs, tissues or stem cells, is the way to be able to overcome the new set of problems medicine seems to be facing.

How do we do the protection of cells? Well you've probably seen a lot in the lay press, but also in the medical literature of using antioxidants to protect against the damage done by free radicals – whether it's beta-carotene, or co-enzyme Q, or pomegranate juice, whatever you're using, these are the kinds of things people are using to try to prevent free radicals from damaging their cells. And there's some kind of evidence that this actually might be effective. Extreme caloric restriction has been shown in animals to really get them almost to starvation levels, at least in rodents, has been able to potentially increase their life spans as much as 30% or even in some cases as much as close to a 50% increase in the life span of those organisms.

People have been manipulating genes so that in nematode worms there's a daf-16, a transcription factor in daf-2 which inhibits a daf-16, and if you manipulate these, and a woman named Kenyon at UCFS has been able to do this, she can get these worms to live 3 and a half times as long as they would naturally, just by manipulating these genes. For humans that would mean a maximum life span of 350 years. That's what's being talked about, and it's been done for nematode worms.

Yeast? People have shown that if you get an over expression of what's called the sir-2 gene, you can get a longer life span. In fact, people have shown that it's probably this that happens in extreme caloric restriction, as you get more of this sir-2 gene, and why bother dieting if you can just manipulate the gene, people are suggesting.

There are ways people have talked about preventing the loss of regenerative capacity. If I told you that the chromosomes shorten, well they are talking about ways we can molecularly cap these ends of the chromosomes and prevent them from shortening. Or we might be able to enhance the expression of an enzyme that actually repairs the ends of these chromosomes. It's called telomerase. And then of course what's gotten much more in the press is stem cells, as the root to doing this. So I want to make sure everyone is clear as to what stem cells are and how they work.

Stem cells are precursor cells. They're cells that are in everybody's body that retain the possibility of replicating themselves to proliferate. They're uncommitted in a certain sense. They have not decided that they are going to become, if you'll excuse the anthropomorphism, an eye cell or a skin cell or a tooth cell. They're uncommitted, but can be committed to being one of these very specific cell types if they develop in the proper way. And there are 3 terms that are used in describing these: Totipotency means a stem cell that could in fact be any cell in the body. In fact, could become another entire organism. Pluripotency means that it could become a variety of tissues not necessarily an entire organ, and the most pluripotency is that there are 3 basic from embryology, and Dr. Pravitz could tell us much more about that, but there are 3 layers within the embryo – endoderm, mesoderm, and ectoderm, - and these can go on, and these are the stem cells, can go on to become, from the endoderm, basically gut, mesoderm, things like muscle and heart, and ectoderm things like skin and brain cells, so they have the potential to differentiate within those lines any of those kinds of cells. And then there are more tissue-specific kinds of stem cells such as bone marrow and blood stem cells.

Now, recently though, you should be aware that some people have been showing that maybe even in the things that we think are already committed to a narrow range of plasticity that could only become a certain kind of tissue, maybe capable of being de-differentiated back to a point of which they could become stem cells of various other types. So there's evidence not that bone marrow mesenchymal stem cells could be brought back not to totipotency but to pluripotency to become cells that could be either endoderm or ectoderm or mesoderm. And if you can do that, if you can walk a cell back to the point where it can do that, it can become any tissue in any of our bodies or any other organism. This has been shown in mice and in humans. I will say it's not 100% proven. Not everybody believes that it's not artifactual. Most people accept that it seems to be possible.

And where can you get stem cells? There are basically two categories. One is called adult stem cells, and the other embryonic stem cells that are out there in the basic literature. But adult stem cell is something of a misnomer. Anybody who's been born, even an infant, stem cells coming from that individual would be adult stem cells, so just be careful of that language. You can get adult stem cells from the bone marrow of any of us. They've been found increasingly in places where we thought they wouldn't be. In the liver, actually some have found them in the brain, and a rich source of them, and these are called again something of a misnomer, adult stem cells, from umbilical cord blood, a rich source of fairly pluripotent stem cells in umbilical cord blood.

The other source is embryonic stem cells, and there are 3 ways basically people have said you can get them. One is to use the frozen embryos that are left over from in vitro fertilization. The other would be to do in vitro fertilization solely to create an embryo to get the stem cells from it. And the last source would be to clone, to create a clone of an individual to get the source of stem cells.

Just to go through some basic biology, the usual way this works and the very earliest stages that you get a sperm and an egg to come together that could either be naturally or through in vitro fertilization to form a zygote. Or you can clone to form a zygote, but you need to start, at least thus far, with a zygote. That zygote begins then to divide, and when it gets to the blastocyst stage, the inner part of it, what's called the inner cell mass, that inner section is where the stem cells are that are taken out to create the embryonic stem cells that are proposed to be used for therapeutic purposes, or at least to experiment for therapeutic purposes. If it's implanted or if it's already developing inside a human being, it then would implant into the wall of the uterus, and by 14 days you've got an embryo. That's the basic way in which Biology 101 things happen.

Just so we're clear about the term cloning, again the only way we actually do that these days is something called somatic cell nuclear transfer. Just so you know how it works, what one does is to take a human egg or that of any animal, and take the nucleus outside of that egg, take it out, and just leave the cell, the sack of cytoplasm with a membrane, and then you take a somatic cell, an adult cell from your blood, or your bone marrow or your cheek, wherever it would come from, and you take the nucleus out of that adult stem cell, and put it into the egg's cytoplasm to create a clonal zygote. That's the way in which this is technically done. It has been done in lots of mammals. Up until a few weeks ago most of us believed that it had been

done in human beings, but we now actually know that there was a great scandal, that the Koreans who claimed to have done this actually did not accomplish it. So it has not yet been done in human beings.

So what's being proposed? And with all that as basic science, what are we trying to talk about today? We wanted to get away from the question, the vexatious questions of how it is that we're going to get the stem cells, but let's say we get them in a way that all of us would agree is morally okay. And certainly everybody agrees that stem cells from adults as sources are morally unproblematic as sources of them. The question then becomes, what are people proposing to do with them, and are there any ethical questions to ask about that. To take a step beyond whether we're killing embryos to the question of how we're going to use stem cells no matter where we get them. And this is from the web site of the School of Medicine of Emory College, London, and their Institute on Regenerative Medicine, and they say, "The new field of tissue engineering brings together for the first time the scientific disciplines of biology, material science, and biomedical engineering directed towards long term repair and replacement of failing human tissues and organs. Living cells are harvested, grown in the laboratory, often on an appropriate scaffolding, and stimulated to perform specific tissues that mimic the complex structures and physiological behavior of natural tissues, and ultimately spare parts developed in the laboratory can then be put into a patient either by injection of cells or by the implantation of intact tissue or an entire organ." That's the question that we want to look at more. What are we going to do with these stem cells? This is what's being proposed.

Here's a quote from *The New York Times*. Just a month ago, a very reputable scientist from the University of California at Irvine, Michael Rose, was interviewed and asked, "Do you believe there is such a thing as a limited life span for humans?" His answer to the reporter was, "No, lifespan is totally tunable. In my lab I tune it up and down all the time. I do it for fruit flies; there's no reason in principle we can't start doing it for human beings." And then we get progressively more into the commercial aspects of this. William Hazeltine, the CEO of Human Genome Sciences boasts, "I believe our generation will be the first to map a possible route to individual immortality." And then, even more complex, I just got this email two days ago, "The Anti-Aging Medicine World Congress", if you want to go to Paris in 2006 you can sign up, they anticipate a lot more people than are here today – 2,500 participants from 80 countries to come to this – the Anti-Aging and Esthetic Medicine for Global Patient Management. So these are the kinds of things people are talking about.

Now what are the questions that we might want to ask about this? Well, the ethical questions, we usually say we have a duty of beneficence to help our patients and some of this is already being done and I'll tell you that for instance that umbilical cord blood transplants have been put into children with a devastating genetic defect called Hunter Hurler Syndrome. They used to all be dead within a year or two. Now they so far seem normal in development and in other aspects up to 7 or 8 years of age after having had this done. People are talking about and people in our own medical school have shown this in mouse models, and are working on it in human beings, taking bone marrow stem cells and putting them into the blood of people who've had heart attacks, and showing that those stem cells go to the heart and transform not into scar, but into new heart muscle tissue. People are talking about, although there's been less success here, about repairing damaged neuronal tissue, use stem cells to repair people who've had cord transections from trauma or for strokes, or using stem cells to treat degenerative disorders, again much less actual success here, but people are working on it to treat Parkinson's Disease or Alzheimer's, diseases of the brain, but also doing stem cell transplants of the islet cells, of cells that go on to become islet cells to replace those that are damaged in type 1 diabetes. People are even talking about doing this to prevent atherosclerosis, and in fact there's a trial going on at John Hopkins and Duke in which they're saying is what happens in atherosclerosis is that the damage from high blood pressure and cholesterol building up in your arteries is always being continually repaired. This is a dynamic process. And what happens is that as you get older, the repair mechanism, the stem cells that do the repair and replace the damaged artery start to not be able to do that and then the balance is tipped in favor of plaque building up and not the repair process and that's when they're damaged. So if we could just put stem cells into everybody, they wouldn't get heart attacks. That's the idea. And people even use them to repair things like damaged cartilage. They say, why do a joint replacement if you can just put in stem cells and replace the damaged cartilage from osteoarthritis?

There are scientific questions people have raised about this that you should be aware of. For instance, animals without telomeres, if you think, oh, we can solve this just by capping the telomeres and giving

people telomerase. Well, animals without telomeres still have limited cell divisions. Genes, one gene, one polypeptide is certainly gone. But even one polypeptide and one gene may have multiple different kinds of functions, and the more advanced the organism is, the more complex the things the genes do. So the thought that we can just manipulate one gene or not has some people skeptical and they say you might do that in a fruit fly or yeast, but you're not going to do that in a human being.

Using embryonic stem cells, in the animal experiments at least, they seem to have a high predilection for forming tumors if you put them into animals, tumors called teratomas. And people worry about whether if we put these into people, and we make a mistake and they are part of the germ line or if we manipulate somebody's genes and it's part of the germ line and if we make a mistake, then it becomes heritable; we're created a disease that is not only affecting the individual but is passed on to their progeny. So those are some of the scientific questions that have been raised.

Metaphysical questions get raised about some of this. People worry about genetic reductionism. I've actually heard one person say, a good Aristotelian, that if Aristotle were around today he's say that the genes must be what he thought of as the soul of the organism. That's an Aristotelian soul. We used to say that nothing was certain but death and taxes; a lot of people are questioning that. There are people who are saying that we can take evolution into our own hands. We are the organism, the kind of thing that can control our own evolution, and if we've got the potential, why don't we do that? Is there a difference between indefinite ongoing-ness, just keeping yourself going as a biological organism, and something some of the rest of us might call eternity. Are those the same thing? What does this do to medicine? Does it alter medicine as a praxis? Does it change its goals in any way?

And then ethical questions. Part of it is the distinction between therapy for diseases and enhancement. And it's not unique to regenerative medicine that there are some people who question if it's ethically relevant at all. We get into the ethics of the question of prevention if we use this to prevent diseases. People raise questions about whether it's a good thing to live indefinitely. Leon Kass certainly makes one point of saying, well, just as you get things done like a talk like this at the last minute, having the pressure of a deadline, what if you had no deadlines in life? Would you have the same ambition to do things? What questions does this raise even if we begin to raise the lifespan by 20 years? What does this do to intergenerational relationships? Who's going to pay for the retirement funds if you still retire at 65 and live to be 125? These are questions that we seriously have to think about.

And then questions about justice. In the allocation of funds for research, is this really where we want to go? What do we talk about in terms of our allocation for global health justice as well? I'm not going to answer those questions for you. I'm going to leave that to our two very distinguished speakers. I simply wanted to give an overview and raise the questions. We'll have lots of time to chew on this. Thank you.

Lynn: Our next distinguished speaker is Daniel Callahan. Dr. Callahan was the co-founder of the Hastings Center in 1959, and he continues on there currently serving as the Director of the International Program. His interests range widely, but in recent years he has concentrated on health policy and research policy. Dr. Callahan is the senior fellow at Harvard Medical School and serves as an honorary faculty member of the Charles University Medical School in Prague. Dr. Callahan received his Ph.D. in philosophy from Harvard, an MA from Georgetown University, and his BA from Yale. He holds 4 honorary degrees. He is a member of the Institute of Medicine in the National Academy of Science, and, in 1996, won the Freedom and Scientific Responsibility Award of the American Association for the Advancement of Science. He's the author or editor of 36 books, including, the one more relevant for today's discussion, *The Research Imperative: What Price Better Health?* He's also contributed articles to numerous journals including *Harpers*, *The Atlantic*, *The New England Journal of Medicine*, *Jama*, *The New Republic*, and a variety of other journals. Today Dr. Callahan will share his thoughts on the research community, society, and regenerative medicine. Join me in welcoming Dr. Callahan.

Callahan: I need to get some water first. Thank you very much. It's a pleasure to be here. I've known Dan Sulmasy for a number of years now. It's always a pleasure to work with him. I've known Ed Pellegrino for an even longer number of years and it's a delight – I don't know if we've ever been on a program together over all these years, but possibly so.

Let me give a little background of my recent issues. I have been particularly concerned with health care reform, but not in a usual way. I come at the health care reform something of a philosopher. Most discussion of health care reform would be turned on various different ways of organizing and managing the system. President Bush is pushing medical savings account at the moment, a lot of people are interested in information technology, evidence-based medicine. They're all sorts of ideas about how to reform health care. Similar discussions are going on in Europe. What's been striking to me, however, is that the foundations of health care have not been examined in any very profound way. My question has been, before we can talk about questions of justice or organization, we have to ask the fundamental questions: Where do we think health care should be going? What should be the appropriate ends of medicine given many of the advances that Dr. Sulmasy has presented? And how can we get a deeper discussion into the management discussion? And I think Americans peculiarly believe that all problems can be solved if we simply manage things better, and hence the effort has been really to evade the deeper questions in many ways, to focus on that.

Now the angle that I bring to this particular issue today is that I really want to ask a fundamental question, and using regenerative medicine as a kind of case study. That is to say, in thinking of that regenerative medicine, we're really being forced to say where we think health care ought to be going in the future, if we had our druthers, if the research works at it. And I think in order to answer that question we then have to ask some fundamental questions about the nature of human suffering, the nature of human community, and just what is it in the long run that will do us good as a community.

Let me start in on this issue with a little quotation. In 1972, the Kennedy Center for Bioethics was founded and there was a wonderful event there. One of my dinner partners was Joshua Letterberg, a Nobel Lauriat up the street there at Rockefeller University, and he said to me, I don't remember the context at all, but he said the following: "If we don't carry out medical research, the blood of those who die will be on our hands." Interestingly, Irving Weissman, one of the major figures in stem cell research, said almost the identical thing. At the time, I wasn't interested in these matters, but I thought that was really very interesting. For instance, if a legislator decides to put more money in education this year, and takes some away from health care, it puts the blood of those who might have been helped on his hands. It immediately raised some questions. But I dropped the issue for some time, but recently, as I began looking at the direction of biomedical research and health care reform, I began catching more and more the flavor of a kind of moral obligation behind research, an obligation that simply should not be avoided under any circumstances, and, moreover, it is so important that it should trump other social needs. This somehow is one of the great, most important tasks for human life.

Now this will stimulate in great part by looking at one of the budgets of the National Institute of Health. This year for the first time since 1970 the National Institute of Health will actually see a decline in its budget, a very tiny decline, just a few hundred million dollars, but for them, a symbolic decline because it's been one of the few federal agencies that has always had an increased budget. It has always had bipartisan support and for the most part has been one of the least criticized of all federal agencies. When the republicans talk about the big government, they're usually not talking about the National Institute of Health.

Now, the interesting question. This to me culturally says something about the place and importance of biomedical research in American life. Other nations do not invest the kind of money in research that we do, and I think this is a peculiar, interesting American trait.

Secondly, if one looks at the history of biomedical research over the years, the flavor begins to change. Up until the late 19th Century, research was not even taken very seriously. The Germans were doing a lot of work in research, but Americans were not following suit, but the catch-up was underway. By the end of the 19th Century, research had firmly established itself in the United States. And it increased during the first part of the 20th Century, and with the establishment of the NIH in 1937, it increased very rapidly thereafter.

What is clear if one looks at the rhetoric of research, to me the most striking change in rhetoric was that somewhere in the 1960s, maybe by the 1970s, the language of war was beginning to be used, and President Nixon talked about the need for a "war on cancer." This sort of symbolized a raising the stakes constantly.

It was just a wonderful thing to do research earlier on, but now, my gosh, let's really take this seriously and begin declaring a kind of warfare.

The stem cell debate has seen this very strongly, and the typical way the stem cell debate has been cast is one of balancing, on the one hand, the rights and moral status of the embryo over, on the other hand, all of the lives that could be saved if this research is worked at. Also, interestingly, you will find a sort of similar argument in the rhetoric of the pharmaceutical industry. Its argument is that yes, we do charge high prices, yes, we know they're a burden, but by God they're necessary because we are doing the research that's going to save future lives. And they have used that as a mantra for many years now very successfully. This is one of the few countries in the world that does not control drug prices and I think in great part because they've made at least a publicly acceptable kind of argument. Interestingly, they don't ask the question, well, I guess if you use some of your profits to pay for the use of the drugs for HIV disease, you could save lots of lives now. Why is it that the saving of lives now is more important than the future lives that would be saved by the higher prices so we can do the research? In any case, I see a threat running through all of this.

Now, what's culturally going on here? I think, very strikingly, if people of all ages have seen illness and death as evils and bringing suffering, I think we have even increased the importance of that idea so that suffering and illness are now even given a higher status I believe than they were earlier on. One peculiar feature about health care spending is the fact that by every possible standard people are living longer lives, the elderly are having fewer disabilities, the mortality rates of practically every lethal disease is declining, and yet, at the same time, as things are actually getting better, we spend more money. No one ever seems to stop to think, Gosh, maybe we're spending enough. We're making great progress. The healthier we get, the more health we want, and that's to me part of the problem of defining health policy.

I think it's also the case that one enormous cultural change is that we are really seeing a very radical decline in fatalism. I think earlier generations felt people were going to die, that's the way it was. You could have a religious reason for that or a secular reason, but people died. That was simply a fact of life, and I think there's now a very significant decline in that kind of fatalism. A kind of new optimism is that medicine can do things now that were not even imaginable earlier. There's a wonderful quotation by the political scientist, Michael Wall, from some years ago, which I think really catches this very nicely: "What has happened in the modern world," he writes, "is simply that deep disease itself, even when it is endemic rather than epidemic, has come to be seen as the plague. And since the plague can be dealt with, it must be dealt with. People will not endure what they no longer believe they have to endure." Well, that I think is very powerful.

Finally, and I think particularly in this country, it's pretty obvious that basic medical research, not to mention health care delivery, is a source of enormous business and enormous profit. The great difference between, one thing very striking about the people supporting stem cell research is that not only is there a lot of scientific support, public support, but there's an awful lot of money to be made for this kind of medicine, and that in itself is a valuable thing because health care and medical research provide jobs, they provide export goods, they do all sorts of good things economically, and this is a kind of add-on to the direct human benefits.

Now, I'd really like to make sort of 3 arguments with that as a little background. First of all, I don't believe in general there is any moral imperative, moral duty, or moral obligation pursued in medical research with the exception of one situation, namely plagues and epidemics where large numbers of people are killed, where the disease is spread, and where particularly the infrastructure of society, that is to say the young working people, that whole middle age range group, if you will, are destroyed. And that's what makes AIDS such a peculiarly awful disease. It affects younger people. I spent last night reading this book that will scare the lights out of you. The great influenza, and what was very striking about the 1980 influenza epidemic which amazed everyone is that it didn't get the elderly people who were thought most at risk. It was younger people, in their 20s. It started very heavily in military camps, and spread from there. But it was young people, and this was really scary because in many cases whole towns collapsed because all the people who ran them, the young people who were in charge of everything, they died and everything else

thereafter collapsed. So I think any research that deals with endemic diseases seems to me absolutely imperative.

Beyond that, and here again there are a lot of diseases – cancer, heart disease and stroke, that primarily affect an older generation, that certainly are costly for society, but one can ask the question, to what extent is our society at present burdened by the fact that people die of cancer? We know that individually we're burdened. I use cancer as my example because that's a disease that runs in my family. But I guess the question that I would ask from a communitarian point of view: Is this ruining our country? And I think the answer is "no." It's terrible, it's a bad thing, but it is not ruining our country. The fact that people die from old fashioned diseases does not ruin a country though endemics could ruin a country. So that is one question: How do we want to think of those diseases, that many are gone after by regenerative medicine? Regenerative medicine has also gone after Parkinson's, after Alzheimer's, things that not only kill people, Parkinson's doesn't necessarily, but certainly Alzheimer's in the long run, but make life miserable. Those seem to fall under different categories, along, say, with mental health, things that actually do us in totally.

So first our claim seems to be that it's very difficult to make a case for moral obligations in research. Secondly, one difficulty in balancing the common language in the stem cell debate is how do we "balance"? And many issues have been balancing issues. The issue of human suffering, and research is always put also in terms of a balance. And how do you balance the rights and the need to protect subjects over against all the lives that could be saved if we could carry out the research? Interestingly, to me that's the fascinating example of that case. That's one area where over about a century, but particularly after the Second World War was generally concluded by the medical and research that you may not carry out research on informed subjects, on competent subjects, without their informed consent, and we don't care how many lives you could save if you violate that principle. So it's one of the cleanest, purest principles you'll find around in modern research. To me, it's a striking example. One might ask the question, well, if human subject research is caught up in the stem cell debate to the same degree, would people again say, would they want to get rid of the informed consent to save all the lives? But at least historically that's a great little case study itself.

Now, I guess the way I'd like to think about the question of deciding what we need in regenerative medicine is a perfectly fine example of that is by asking the question, what does the community need in the long run to flourish? And it seems to me that there are many things that communities need to flourish, and one of the great difficulties, I think, about the research imperative, is somehow the notion that it trumps everything else. Now my argument would be that health, well certainly fundamentalists I've heard all my life, without health, you've got nothing else, - well that simply isn't true. In a good society you need education, you need jobs, you need defense, you need a whole range of things without which society can not flourish. It's absolutely useless to be in great health if you stand a good chance of getting mugged, raped, or murdered. It's absolutely useless to be in good health if you stand in danger of war, terrorists, or other sorts of things coming into your life from the outside. We all need nutrition, we all need good housing. There are a lot of things. Health is one of the important ones. With bad health, it's true, you can't have anything else. On the other hand, without good nutrition, you can't get much else either.

So, I suppose the question I want to raise is: what is the appropriate role of health amidst all of the other things? And what do you do particularly when you get along in a massive campaign as regenerative medicine, which really says, look, there are no better ways to spend our research money and, in a way, there's no better way to spend money itself more generally on medical research. I want to answer, so what? Or, is that true? It was the case about 40 years ago that about 6% of our gross domestic product went to defense. It was during the Cold War, 6% to education, 6% to health care. We now spend less than 6% on defense, education is still around 6%, health care has gone to 16% of the GDP. Now the question is, does this make sense? Is this a good ratio?

I love to come to New York because as I sometimes tell out-of-towners, New York's an interesting city. If you need a heart transplant, and you can find the organ, you can probably get it. You get it paid for free, and you're going to be treated by wonderful hospitals, by highly-paid, well-trained specialists, but walk down the street one block and you come to lousy schools, buildings falling down, lacking textbooks, all sorts of things wrong. And one wants to answer again, is this the right set of priorities, is this the right

balance? I will say it might be a question of balance. The difficulty with most of these balances, for instance, how do you balance off health care, education, versus anything else? We are talking about apples and oranges. There's no common metric for making such comparisons. The net result is it's normally these issues get settled by popular enthusiasm, money, all sorts of things enter in, and one reason, obviously, is that health care is a much more profitable institution than education. Most of us worry more about getting sick and dying than we do about the quality of education for our kids. It's very hard actually to work up an interest in getting education up to the same place say as health care.

Let me conclude by saying sort of an example about everything I've been trying to say here. During the California debate for the 3 billion dollar bond issue, the papers in California were running some parallel stories. The stories were this: 2.5 million adults are illiterate in Southern California. This means people who have no economic future, many of them immigrants, many of them of course illegal immigrants. They have no economic future. They are going to be stuck forever. But there was no call for a bond drive to help them. And, of course, there are no big business interests that would gain much from working on that problem. But the net result, I would want to argue, would be spending money, that 3 billion dollars, to help that group of people for immediate benefits of a clear kind, is far better than the 3 billion dollars they decided to spend on the venture of stem cell research and regenerative medicine. So I will stop there and say I think we have yet to figure out how to deal with this. We get caught up in the hype and excitement of the new drugs, the new breakthroughs, but I think increasingly as the costs go up for this venture, we really have to ask the fundamental questions that people tend to avoid, don't know what to do with, but they're there and we better think about them. Thank you.

Lynn: Thank you, Dr. Callahan. Our next and final speaker for today, before we get into the panel discussion is the distinguished Dr. Edmund Pellegrino. Dr. Pellegrino is currently the chair of the United States President's Council on Bioethics as well as a professor emeritus of medicine and medical ethics, and adjunct professor of philosophy at Georgetown University. He has served as the Director of the Center of Clinical Bioethics, at Kennedy Institute of Ethics, and the Center for Advanced Study of Ethics at Georgetown. He has also served as President of Catholic University, President of Yale, New Haven Medical Center, Vice President of Health Affairs at the University of Tennessee, Chairman of the Department of Medicine at the University of Kentucky, and Vice President of Health Science Centers at SUNY Stony Brook. From 2004 to 2005, Dr. Pellegrino represented the United States at UNESCO. He is a member of the American College of Physicians. He is a member of the Institute of Medicine of the National Academy of Sciences, and he is a recipient of a number of honorary degrees as well as a recipient of numerous awards, including the Benjamin Rush Award from the AMA. Dr. Pellegrino is the founding editor of *The Journal of Medicine and Philosophy*, and he has authored or co-authored 24 books and, astonishingly, more than 550 articles. Dr. Pellegrino will talk to us today about regenerative medicine and patient care. Again, please join me in welcoming Dr. Pellegrino.

Pellegrino: Thank you very much, Lynn. It's a delight also for me to be here and to join Dan and Dan, both Dan's, Sulmasy and Callahan. Dan, we have been on a program before, but I think you've forgotten because I disagreed with you. Not so, he's a very honest person. It's a delight to be here.

Well, you've heard the scientific foundations of this new entity, more than a new entity perhaps of regenerative medicine. And you've heard the social dimensions. I'm going to take it down to the clinical area to the conduit through which, one way or the other, all of these wonders are going to have to funnel, and that is to the physician/patient relationship, and some of the ethical issues that are generated by such a thing as regenerative medicine. I call it a neologism, which it is, and therefore it's come upon me to define it. Dan Sulmasy laid out the range of definitions, but the one that I'm going to use is: Regenerative medicine is medicine which is directed primarily at the repair, restitution of functional impairments in organ systems and tissues using a variety of methods which are listed on the board, involving recent advances in cellular biology, genomics and nanotechnology, to mention a few.

I want to make an assumption that regenerative medicine is going to come, and second, that it will be effective, at least in part, but also, it might be effective all the way. And by a series of episodes of repair of our tissues, whether by aging or any other disease process we achieve virtual or actual immortality. I think that's the aim in the mind of many of the people who are engaged in this field today, and so I want to look

at it from the point of view of the possibility of longevity and compare that with some of the other uses of regenerative medicine. I'm going to do it in the following way: First, I want to describe something about the physician/patient relationship and what the fundamental moral commitment there must be. And then secondly, the forces acting on the physician in that relationship and the ethical issues generated by having or being a conduit of such powerful techniques as you saw illustrated today by Dan Sulmasy.

First of all, let's look at that physician/patient relationship. Really the moment of truth which comes in the moment when the physician and the patient must decide together whether a technique of tissue repair is going to be used, and for what purposes. Very briefly, physicians are consulted by patients because patients want help in disease processes, generally speaking. The physician offers to help, that's his act of profession, or her act of profession, by saying, "What can I do? How can I help you?" Implicit in that declaration, which is a public declaration, an act of profession, is the promise of a) competence, and b) the use of competence in the interest of the patient, not oneself. A promise of non-exploitation. Don't tell me exploitation happens. I know it. I'm talking about the ethics of medicine based on the realities of the relationship.

How does something like regenerative medicine impinge on that obligation which is to act for the good of the patient, and the good of the patient is the physical good, the emotional good, and I happen to believe, in addition, the spiritual good of the patient, if not entirely, at least to take it into account. I'm going to look at the question by listing for you simply some of the conflicts, and I have about 9 or 10 of them here. Mindful of the time limitation imposed upon me. Beware of speaking in the presence of your own graduate students. They take the opportunity to impose on you the rules that you have imposed on them, so viciously and fast that I will obey you, my favorite graduate student.

Let's look at some of the issues. First of all, is regenerative medicine within the purview of the ends and purposes already used to define the relationship, the healing relationship. Well, I think if you look at the list that Dr. Sulmasy gave you, I think it's hard to deny that repairing and restoring function to tissues injured by disease is outside the range of medicine. So that from the point of view of those uses which are therapeutic, I'll just give you 2 examples. The things we can do with a patient who has diabetes, the person has life-long diabetes, has loss of pancreatic function, and ultimately will develop diabetic nephropathy, damage to the kidneys, will develop damage to the heart, will develop damage to the nerve system, and so on. If we can repair those, that surely is therapeutic, for the good of the patient, repairing a defect. One can hardly deny that. But, even if you accept that, how many times do you do it? When does therapy and repair of an organ approach longevity as the major, primary use of the technique? Where is the cut off point, and how do you make it? That's the question we can't answer at this point, but it has a great deal to do with whether or not at some point, even in the therapeutic uses, we extend beyond therapy into what is called enhancement medicine, as Dan has outlined.

Second, if we can achieve longevity for its own purposes, and if we can achieve, let me call it, virtual immortality, virtual in the sense that we don't know where it would end and where it would go, but it would add years, and as has been pointed out, a certain number of years, is that consistent with the ethics of medicine? Should the physician be the handmaiden of biotechnology to the extent of providing that assistance to the patient? I would say, no. It's not consistent with the ends of medicine which for the moment, for the moment, we take to be therapeutic. On the other hand, should we extend medicine beyond therapy, to include enhancement medicine – giving me bigger muscles than I have, more hair than I have, a better nose than I have, etc., to enhance my life, to make me more satisfied with myself? I would say that's a very dubious end, and is not one of the ends, but that pressure would be on your physician do to that for you or for somebody, some member of your family.

Third, is aging a disease? What we do know is that as one becomes older the functional units of the organs begin to drop out. I happen to have been a nephrologist in my past years. I'm very much aware of how these functional units in the kidney drop out with the passage of time. The same happens with the alveoli of the lung, the same happens with the capacity of muscle cells to function, and so on. They wear out, if you want to put it that way, but more than that, they actually decrease in number, and at some point, that whole kidney has to be replaced. Regenerative medicine in one of its forms, tissue engineering, has as its holy grail generation of whole organs outside the body and then transplanting them. How far can we go down

this line? Dan has raised questions of the social impact of that kind of expenditure of funds. I raised the question about how far do we go as physicians in propagating that. You could say, well, we don't need physicians. Tissue engineers will take care of that. That's like the people in favor of assisted suicide saying, "Well, no, the physician doesn't have to do it. The obituaries will do it, the person who creates your obituary by assisting you to go on to the next world. You can't avoid someone doing the functions of the physician whatever you call him. Someone's going to have to say, "This organ is diseased. This is the evidence." Know how to pick it up. And then know how to administer. If you're going to transplant a kidney, you have to know how to do it surgically. There's no way of avoiding medicine. And medicine should not participate again in providing longevity.

In order to do so, what about the obligations of medicine to society? I'm well known for always defending, the individual patient, and the importance of the obligation of the physician to the good of the patient. However, there comes a time when physicians' individual actions have an impact on the whole of society. What would've happened if we would have indulged in this activity as physicians, and add to the population by continuing a life for those people who could pay for it repeatedly? And that's another problem of justice, which is of course an obvious one. But what would happen if we could give them immortality. Is this a good? Can we say we're acting for the good of the patient? That's a metaphysical question, and at the end it will be acknowledged, I'm sure. What is the purpose and meaning of human life, and where do we fit in with our obligation, our promise at the very outset when you are coming into my office, by saying, "What can I do for you?" Your assumption is that I will act in your good and is longevity a good? For those of you who are familiar with Jonathan Swift or Anthony Trollop, read what an imaginative writer would say about having the gift, or the bane or the burden of immortality. Would we be creating dystopia or utopia? The utopia of living forever, the dystopia of living forever. We don't know the answer to that. But clearly there will be some point at which too many people on this earth, exhausting its resources, will result in, I would suggest, total social disorder.

What about the physician participating in research, or even in therapeutics when there are so many scientific questions unresolved at this particular moment? From my point of view I think the most fearful is that thin line between cell proliferation, cell differentiation, and unrestrained cell growth, malignancy. I think that's been totally neglected in the whole stem cell research possibility. We don't know, and especially now when people are talking that the source for the stem cells that might be used in regenerating tissues would come from teratomas. For those of you who are not physicians, teratomas are bizarre kinds of tumors that grow in a disorganized fashion. You can't recognize a total organism, but you can recognize teeth and skin and hair in a mass, and they want to take those cells. But again, scientific research, my own work includes work in a laboratory, not to mention clinical investigation. I have a great regard for science, but the science here is very shaky. To what extent does the physician go along with this? Does he participate in the research? There's a great deal of drama and seductivity about participating in research.

A major problem today is the falsification of research by physicians who practice or are induced by pharmaceutical companies to do research. What are our responsibilities here? These weigh on the physician. They weigh at that call, at the point, at the moment of truth when we decide for and with this patient what is to be done here and now. Tissue engineers can't replace us.

What about the participation of physicians, and here I'm going to get into trouble, but I'll raise the question, in the commercial dimensions of regenerative medicine? It's going to be very lucrative. You've heard of Hazeltine, the president of one of the companies, he's the one who invented the term, "Hurly Grail" for doing whole organs; it's a very attractive idea. As I said, if someone were to die at age 18 of diabetic kidney disease, certainly we'd want to replace that organ, and we'd take that organ wherever it comes from, so long as the source of cells does not come from the human embryo. Obviously that's a limitation to some of us which must never be breached.

We get down here then to the fundamental questions. We can not answer those critical, day by day, physician/patient relationship questions, the ethical issues that face us, without looking at the ultimate questions. And that creates a problem. We physicians are thrown into the middle of decision making when the ultimate questions have not been answered. What is the meaning of human life? Why are we here? Is it to live forever? Is that a good for humans? In Aristotle's sense, does that mean humans flourish if they live

forever? We all seem to think that. Some of us, clearly, some of us will ultimately reject this, others might think of greater subjects of wisdom, those who want it. But nonetheless, the pressure will be there, and we need to answer the questions.

Just let me close. Is the dilemma a true dilemma, or is it really a conflict of duties? Kant described a true dilemma as an impossibility, and I'm inclined to agree with him because a true dilemma says, and everybody calls all the questions and ethics a dilemma, and that's a misnomer. A dilemma is when you're obliged to do X and you're obliged to do Y, and if you do X, you can't do Y, and if you do Y, you can't do X. As Alan Donegan says, I think the issue is not a dilemma, it's a conflict, not of obligations, but of the grounds of obligations. And now we can step back and look at it. There is a way of looking at it. The grounds of the obligations. Why do we have obligations for therapy? Why do we have obligations to use various techniques, and which ones take precedence over the others? You can't resolve a conflict of that kind without putting some kind of order which takes us back to the question of what does it mean to be human? And that's a tough question, but I think we have to keep that question always in the background.

So it's time that we debate the public issues, not play catch up ball, which is always happening in technology moving ahead of ethics, raising those questions now, and, I hope, following the precautionary principle. One does not act when things are so doubtful that the dangers may well outweigh the putative benefits, no matter how big the benefits are, or when the ethical issues involved are so momentous that they cannot be outweighed by the benefits. Utilitarianism will not work.

Let me close my remarks. I did what I hope Dan was hoping for, to raise questions for a subsequent discussion, and make the disclaimer I must make today. Everything I say, I have been speaking in the name of Ed Pellegrino; it had no relationship to the President's Council on Bioethics. They have not discussed these issues. They have not discussed them in the terms that I've been using, nor with the vigor that I've been using. They have not any idea what I'm saying. So this is exactly only my opinion and you can tear it apart as you see fit. Thank you.

Synthesis

Sulmasy: We're running close to the end, and I was asked to sort of try to bring this to some sort of closure, and of course, trying to anticipate this ahead of time is difficult, so what I tried to do was to just create sort of a basic framework and see if I could fit some of our discussion into this framework. Again, it's difficult to summarize such a rich discussion, and I think there's a lot more that we could discuss fruitfully in the dialogue here. But let me say that at the very least I think we've all talked about some scientific skepticism, particularly about the longevity part of this. I'll recommend one of the last books that I've read which I think is wonderful if you're interested in philosophy and science, *What Genes Can't Do* by Lenny Moss who is a molecular biologist with a PhD in philosophy, now on the faculty at the University of Notre Dame who really tries to counter the argument that genes are in fact somehow the essence of organisms. As others have said before - life invented DNA, DNA didn't invent life. And I think we've got to bear this in mind as we look at all of these various scientific proposals. Genes do more than one thing, so these simple ideas that we're just going to turn one gene on or turn another off and live for 150 years are really from most scientists' point of view fundamentally naive. Even if we do something like we'll fix the telomere problem, we know that organisms that don't have telomeres still age. Human cloning we know is further away than anybody actually thought. We thought that it had already happened. I think we have to bear in mind, and Dr. Pellegrino mentioned some of this in terms of possible negative consequences of introducing these techniques. Carl Popper, the philosopher of science, talked about "the law of unintended consequences" and I think there's a lot we could learn from being cautious about that. And Michael J. Fox may be looking for his cure, and I would love to be able to offer it to him, but I don't think that regenerative medicine is going to be the answer for him in his lifetime. People will say, well, what if it's a one-in-a-million chance? - really pressing this. Well, governments sell lottery tickets, but they don't buy them. And I think we've got to be very cautious about where we, again, put the emphasis in terms of our research.

But to sort of look at the ethical overview, and this is part of what I was suggesting in my response to Dr. O'Connell, let me just sort of take a step back and talk about 3 orders of value that I'll call transcendental, existential and transcendent. What I mean by the transcendental is not what most people mean by it. I mean

by it, what cuts across categories, more in a Kantian sense of what that word is. Nothing to do with transcendental meditation, and not to do with what's beyond us, but what cuts across categories. And we talk about values of a kind that we might talk about being itself, or freedom, in this sort of a sense. There's an existential level of value as well, where we live our lives as human beings and pleasure and pain, joy and suffering, the right and wrong of our acts, and as I mentioned before, I think there's also a transcendent level of value, whether you're a person of faith or not, as a human being, you ask questions like: Where do I place my faith? Where do I ultimately have hope? What's the ultimate object of my love? And those are sort of 3 very different orders of value, and I think they're all at stake when we talk about life as a value. There's a transcendental sense of life having value as being, particularly the being of human beings. There's an existential value to the value of life when we look at it biologically, psychologically and socially. But there's also a transcendent level to our experience of the value of life. It's: What's the point of it? Where is it headed? What are we looking for? Where do our desires as human beings lead us? And these are not commensurable. So when we talk about something like the value of life, I think we often will talk about these values in a transcendental way when we can come up with some pretty absolute norms like: do not kill, do not sell yourself into slavery – violations, transgressions against freedom, and against life as a good for us in its richness for us as human beings in its very essence.

There are also these finite norms we get when we talk about the value of life in an existential way. We want to, as Aquinas said, "Do good and avoid evil." We don't want to abuse the biological, the psychological and the social, but in the end we don't want to worship the biological, the psychological and the social because there is a transcendent value to our life as persons, lived persons, living persons who look beyond both the transcendental and the existential.

And so, I think if we apply it to questions of regenerative medicine, part of what we talked about and at least Dr. Pellegrino and I would suggest that the transcendental value of life, being, where we talk about dignity in a sort of intrinsic sense would say that we don't, there's an absolute and we don't destroy life in order to serve human life. But most of what we do, most of what we're talking about here is at an existential level of value of life, and here very much we have the scientists saying, yes, we want to treat diseases and we can use regenerative medicine to do that. I think we need to be a little more cautious sometimes than we are about how far we take the existential value of preventing diseases, how far we go with that. I think you've heard lots about how we should be extremely wary about enhancement and extension if they're aimed at as aims in themselves, and we shouldn't ignore concerns of justice and prudence in how we do this. So, it leads to a tentative conclusion for me that at least for the present, if not for the indeterminate future, that pursuing life extension as a value in itself may be morally problematic. And certainly worshipping that, sort of thinking that we solve the problems of the human heart by living longer, ignores the transcendent aspects of our lives as human beings.

Now I'll just end with a painting that I saw in Barcelona this summer at the European Society for Philosophy and Medicine which was held in that city. Anybody who thinks that this is not a contemporary artists just because they can't actually paint, this is a Picasso. It was done when he was about 17 or 18 years old. Picasso knew how to paint realistic paintings. And this is called *Ciencia y Caridad*, Science and Charity. I think part of what you see here is a sense in which the physician in maybe too scientific an aspect may be holding the pulse, but is looking at the watch, looking at what's measurable, looking at time, maybe extending time, but concerned with measurement, with objectivity, where we can get into saying, well, it's always better if it's longer, faster, bigger, more. These are the ways in which we look at it. But I think you have within this painting also the sister, the nurse, who's looking at the person in a complete sense that I think includes the existential, but also includes the transcendent and the transcendental. And that as a framework for evaluating questions like this, maybe that's a helpful way to sort of put together some of what we've looked at. It doesn't give you the answers, but maybe it's a way to think about the ends and goals of medicine, the ways in which we ought to carry out our goals in a just society.

I want to thank our speakers tremendously. We are really blessed to have had both Dan Callahan and Ed Pellegrino here today. They gave wonderful presentations. As many of you know they're among the founders of the field of bioethics as much as at least one of them might deny being a bioethicist, and I'll ask you to join me in applause in thanking them.

**transcript not reviewed by the speakers*

